UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,454	06/11/2001	Mervyn J. Monteiro	4115-161	2105

23448 7590 02/10/2004

INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
RESEARCH TRIANGLE PARK, NC 27709

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/878,454	MONTEIRO ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,9,12,23-25,27,28 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9,12,23-25,27,28 and 33-34* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancel claim 4, and adds new claims 33-35, which are related to claims 1,2,9,12, 23-25, 27-28 and are not new matter.

Accordingly, claims 1,2,9,12, 23-25, 27-28, 33-35 are being examined, wherein claims 1,2,9,12, 23-25, 27-28, 33-35 are examined only to the extent of a mutation at positions 116-128 of the EF calcium binding hand. It is noted that part of the new claim 35, drawn to a replacement at residue 172 has been withdrawn from consideration as being drawn to non-elected species.

The following are the remaining rejections.

OBJECTION

Claim 35 is objected to because claim 35 would be allowable, if it does not depend on non-allowable claim 33.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Rejection under 35 USC 112, first paragraph of claims 1, 2, 9 pertaining to lack of enablement for a method for reduce induced apoptosis caused by presenilin 2 in vivo, as contemplated, remains for reasons already of record in paper No.17.

Applicant argues as follows:

Applicant reiterates that Hela cells have been used in studies investigating drugs and other compounds because there is a clear correlation between results found in vitro testing using Hela cells and in vivo testing models. Applicants have provided multiple examples indicating a positive correlation between in vitro results found in Hela cells and in vivo results.

Applicant further argues as follows:

The references cited by the Office discuss cell cultures but a primary or secondary cell culture cannot be compared to immortalized cells such as Hela cells which unlike primary or secondary cells, continue to grow and divide indefinitely in vitro for as long as the correct culture conditions are maintained. Hela cells are the classic example of an immortalized cell line and are adherent cells and not oncogenic in animals, unless transformed by a virus. Specifically, the Drexler, et al. reference, cited by the Office, states at page 3, that the Hodgkin's disease HD cell lines used in the studies were not immortalized cells, and thus, cannot be compared to irnmortalized Hela cells. Embleton, et al;, also cited by the Office, discusses the lack of antigens on cultured cells thereby reducing the accuracy of interpreting results obtained with monoclonal antibodies but the present invention does not include the production of antibodies for the Hela cells or tumor cells but instead antibodies are raised for epitopes on calmyrin. Thus, the Embleton, et al reference is not relevant to the presently claimed invention. The Office further cites Freshney that discusses the disadvantages of in vitro cell cultures and states that cellular metabolism may be more constant in in vitro than in vivo. However, it must be recognized by the Office that Fresney further states that any

inconsistency in the cell cultures can be rectified by inclusion of a number of different hormones in the culture media. Hsu, also cited by the Office, discusses different analysis for monitoring cell population by the chromosome constitution of the in vitro cell line. However, applicants do not even consider the chromosome constitution of the cultured cells as being relevant to the present invention, and instead, as clearly stated in the present application, monitor the level of apoptosis by a simple procedure that can include manual counting of dead cells. Clearly, none of the references cited by the Office provide any definitive proof that in vitro and in vivo test results are not comparable. Likewise, the Office has provided no proof that the overexpression of calmyrin, mutated calmyrin or presenilin altered the cultured cells or its colonization behavior.

Applicant's arguments set forth in paper of 11/12/03 have been considered but are not deemed to be persuasive for the following reasons:

Although there are some similarity between responses to some drugs or to some toxic compounds, or induced levels of some enzyme in Hela cells *in vitro* and *in vivo* models, as recited by Applicant, this cannot be extrapolated to responses of *in vivo* cells to apoptosis signals because *in vivo* responses to different drugs are different and unpredictable, especially when homeostasis regulation and the *in vivo* stability of the mutant of SEQ ID NO:2 are considered, wherein the half life of the mutant of SEQ ID NO:2 (EF-N mutant) used in the claimed method is reduced as compared to the wild type (specification, p.38, second paragraph). There is no indication that the art would

accept that *in vitro* inhibition of apoptosis in Hela cells by any compound as predictive of *in vivo* inhibition of apoptosis in any cell.

In transfected Hela cells, SEQ ID NO:1 and the mutated SEQ ID NO:2 are overexpressed, which is not the case with *in vivo* conditions, wherein PS1, PS2 (SEQ ID NO:1) and SEQ ID NO:2 are expressed at low protein level as disclosed in the specification (p.3, second paragraph, and p.29, lines 1-2). How a cell responds to an apoptotic signal however depends on the intracellular concentrations of a particular family members of proteins that are related to apoptosis (Oltvai et al, of record). Thus an increased or reduced apoptosis could be due to artificial increased levels of SEQ ID NO:1 and 2 in transfected Hela cells.

Further, there is no homeostasis regulation and cell-cell interaction in *in vitro* conditions, that can affect the final response and outcome of a cell *in vivo* (Hsu et al, of record).

In addition, cells in culture have different characteristics, properties, and thus responses to a drug as compared to cells *in vivo* and this difference would be applied to Hela cells as well, which are cells in culture (Drexler et al, Embleton et al, Hsu et al, Freshney et al, and Dermer et al, all of record). The teaching in the art would be relevant and apply to any cell in culture, because due to adaptation to cell culture environment, acquisition or loss of certain properties or certain surface antigen proteins, or chromosomal constitution, i.e. acquisition or loss of expression of genes, would profoundly affect the characteristics, properties and thus responses of cell to a drug, when adapted to culture environment. Thus Applicant's arguments that the references

cited by the Office discuss cell cultures but a primary or secondary cell culture cannot be compared to immortalized cells such as Hela cells is not persuasive.

In summary, there is no indication that the art would accept that *in vitro* inhibition of apoptosis in Hela cells by any compound as predictive of *in vivo* inhibition of apoptosis in any cell.

2. Rejection under 35 USC 112, first paragraph of claims 1,2,9,12, 23-25, 27-28, 33-34, pertaining to lack of enablement for a mutant calcium-binding protein having a substitution at any amino acid residue in the calcium-binding EF hand, comprising amino acid residues 116 to 128 of SEQ ID NO:2, and a method for reducing induced apoptosis caused by presenilin 2, comprising administering said mutant protein, remains for reasons already of record in paper No.17.

Applicant argues as follows:

Applicant argues that the specification teach how to make and use the invention by discussing the exact regions for mutation in the calmyrin protein, i.e. positions 116 to 128 of SEQ ID NO:2, that have been found effective to reduce binding affinity with the presenilins. Applicant argues that Applicant has shown the effectiveness of replacing acidic residues with their amine counterparts so that the affinity for Ca+ would be lowered thereby reducing affinity for presenilin PS2 and reducing apoptosis.

Applicant's arguments set forth in paper of 11/12/03 have been considered but are not deemed to be persuasive for the following reasons:

Applicant has not shown how to use the claimed variants having any type of substitution with any amino acids at any amino acid at positions 116 to 128 of the

calcium binding EF-hand of SEQ ID NO:2, which are capable of functioning as that which is being disclosed.

Although the specification contemplates mutation of any amino acid in the region of the calcium binding EF hands of SEQ ID NO:2, comprising amino acid residues at positions 116 to 128 of SEQ ID NO:2, the only actual example of mutation is the substitution from Aspartic acid 127 to Asparagine 127 of SEQ ID NO:2, which is a conservative substitution. Applicant only shows that a single, conservative substitution at amino acid 127 reduces the apoptosis induced by SP2. This cannot be extrapolated to substitutions at any amino acids in the calcium binding EF hand of calmyrin comprising amino acid residues at positions 116 to 128 of SEQ ID NO:2, or replacing any acidic residues in the calcium binding EF hand of calmyrin with their amine counterparts, because the effect of these substitutions on the function of the contemplated numerous mutants as compared to the Asp127 mutant, and consequently on apoptosis, is unpredictable, in view of the teaching in the art that even a single amino acid substitution or what appear to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein, as taught by Burgess et al, Lazar et al, Tao et al and Gillies et al, all of record. Further, why and how said substitution at amino acid 127 reduces the apoptosis induced by SP is not known. Applicant has not shown that mutation of any amino acid, including amino acid 127 in the calcium binding EF hand of calmyrin comprising amino acid residues at positions 116 to 128 of SEQ ID NO:2 "reduces the binding affinity" between the calmyrin and presenilins thereby reducing apoptosis.

REJECTION UNDER 35 USC 102(a and b)

Claim12 remains rejected under 35 U.S.C. 102(a and b) as being anticipated by Seki N et al, 1998, Saito T et al, 1999, or Naik, MU et al, 1999 for reasons already of record in paper No.17.

Applicant argues as follows:

It is the Office's position that the product of the sequence of the cited reference SEEMS to be the same as the claimed mutant calcium-binding protein of the present invention. Clearly this rejection is based on the possibility that the prior art product MAY inherently have the characteristics of the present invention. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result is not sufficient. (See In re Oelrich, 212 USPQ 323 (CCPA 1981)).

Applicant further argues that the cited references lack enablement and as such cannot be anticipatory.

In addition, Applicant argues that the cited mutation of the 124 amino acid residue is not an amine counterpart of an acidic residue, and thus the reference does not disclose all the elements of the claim.

Applicant's arguments set forth in paper of 11/12/03 have been considered but are not deemed to be persuasive for the following reasons:

The reasons that the language "seems" in the previous statement by the Examiner that "the amino acid sequence taught by Seki N et al, 1998, Saito T et al, 1999, and Naik, MU et al, 1999 seems to be the same as the claimed mutant calcium-

binding protein" was used and is maintained, is because the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Concerning Applicant's argument that the cited references lack enablement and as such cannot be anticipatory, it is noted that the amino acid sequence taught by prior art seems to the same as the claim mutant, and thus inherently would have the same material, structural and functional characteristics of the claimed mutant. Therefore the issue of enablement is not germane here.

Further the limitation that the mutation comprises replacement of an acidic residue with an amine counterpart is not in claim 12, and thus the arguments by Applicant is moot.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

Februrary 06, 2004